Characteristics of Patients with Early Systemic Sclerosis and Severe Gastrointestinal Tract Involvement

EMI NISHIMAGI, AKIKO TOCHIMOTO, YASUSHI KAWAGUCHI, TAKASHI SATOH, MASATAKA KUWANA, KAE TAKAGI, HISAE ICHIDA, TOKIKO KANNO, MAKOTO SOEJIMA, SAYUMI BABA, NAOYUKI KAMATANI, and MASAKO HARA

ABSTRACT. ***Objective.*** To clarify the clinical features of patients with systemic sclerosis (SSc) who developed severe gastrointestinal tract (GIT) involvement in the early stage of the disease.

Methods. Three hundred two consecutive Japanese patients with SSc were investigated: Group 1 comprised 14 patients with severe GIT involvement (malabsorption syndrome and/or pseudo-obstruction) within 2 years of onset of SSc; group 2 consisted of all patients without severe GIT involvement (n = 288); and group 3 consisted of 117 patients without severe GIT involvement within 2 years of onset of SSc. Autoantibodies were evaluated using double immunodiffusion, ELISA, and immunoprecipitation.

Results. We found significant differences in clinical features among the 3 groups. Diffuse cutaneous type, erosive esophagitis, and myositis were more common in group 1 than in group 2 (p = 0.007, 0.003, and 0.003, respectively) or group 3 (p = 0.04, 0.002, and 0.01, respectively), whereas interstitial lung disease (ILD) was more frequent in group 2 (p = 0.005) and group 3 (p = 0.02) versus group 1. Antinuclear antibodies showed a nucleolar pattern significantly more frequently in group 1. Myositis-related autoantibodies, including anti-U1RNP, anti-U3RNP, anti-Ku, and anti–signal recognition particle antibodies, were observed in 57% of group 1.

Conclusion. Our findings strongly suggest the existence of a subgroup of SSc patients with severe GIT involvement in the early stage. Among the Japanese individuals, these patients never developed severe ILD, even though they were classified as having diffuse cutaneous SSc. (J Rheumatol 2007;34:2050–5)

Key Indexing Terms:
SYSTEMIC SCLEROSIS AUTOANTIBODY GASTROINTESTINAL TRACT

Systemic sclerosis (SSc) is a multisystem connective tissue disorder of unknown origin that is characterized by tissue fibrosis, endothelial injury, and autoimmunity[1]. Approximately 90% of patients with SSc develop gastrointestinal tract (GIT) manifestations related to dysmotility[2-4]. Because the pathological hallmark of GIT involvement in SSc is smooth muscle fibrosis, it was believed that GIT manifestations could result from tissue fibrosis[2,5,6]. Replacement of smooth muscle by collagen appears to occur in the absence of inflammatory change and vascular degeneration. Although the mechanisms of impaired GIT motility are not fully understood, it has been hypothesized that alteration in neural function in the GIT is present along with fibrosis in the early stage, leading to smooth muscle atrophy and degeneration that cause severe motility disturbance[7,8]. Recently, it was reported that the neural dysfunction might be due to the autoantibody against type 3 muscarinic acetylcholine receptor[9]. Conversely, in late-stage SSc, severe fibrosis of smooth muscle might be a major cause of GIT dysmotility.

The most commonly affected site in the GIT is the esophagus, which is involved in 80% or more of SSc patients[10]. Small intestine (40%) and large intestine (10%–50%) lesions are also not uncommon[11,12]. Severe manifestations such as malabsorption, repeated episodes of pseudo-obstruction, severe constipation, rectal prolapse, megacolon, and multiple diverticula are rarely observed in both early and late stages[13]. However, we have sometimes encountered patients who developed severe GIT involvement as a main symptom of early SSc, and in some cases the symptom preceded the skin manifestation. Steen and Medsger[14] investigated severe organ involvement in patients with diffuse cutaneous SSc (dcSSc) and demonstrated that severe organ involvement (i.e., heart, lung, GIT) often occurred early in the course of the disease, mostly during the first 3 years, and was closely linked to mortality. They also reported that deaths due to severe organ involvement occurred with equal frequency. The 9-year cumu-

From the Institute of Rheumatology, Tokyo Women's Medical University School of Medicine, and Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.

Dr. Kawaguchi was supported by a systemic sclerosis research grant from the Ministry of Health, Labour and Welfare.

E. Nishimagi, MD, PhD; A. Tochimoto, MD; Y. Kawaguchi, MD, PhD, Assistant Professor; K. Takagi, MD, PhD; H. Ichida, MD; T. Kanno, MD; M. Soejima, MD; S. Baba, MD; N. Kamatani, MD, PhD, Professor; M. Hara, MD, PhD, Professor, Institute of Rheumatology, Tokyo Women's Medical University; T. Satoh, MD; M. Kuwana, MD, PhD, Associate Professor, Rheumatology, Keio University School of Medicine.

Address reprint requests to Dr. Y. Kawaguchi, Institute of Rheumatology, Tokyo Women's Medical University School of Medicine, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan.
E-mail: y-kawa@ior.twmu.ac.jp

Accepted for publication July 5, 2007.

lative survival rate was lowest among patients with severe GIT involvement (15%). These researchers' findings indicate that severe GIT involvement, like other organ involvement [such as interstitial lung disease (ILD), pulmonary hypertension, or renal crisis], might be responsible for mortality. However, clinical characteristics of severe GIT involvement in early SSc have yet to be fully investigated. We examined the clinical features of patients who developed severe GIT involvement in early SSc, and we then determined predictive indicators for severe GIT involvement.

MATERIALS AND METHODS

Patients. Study subjects were 302 consecutive patients with SSc who were admitted to Aoyama Hospital, Tokyo Women's Medical University, between 1992 and 2004. All patients were Japanese and were classified as having dcSSc or limited cutaneous SSc (lcSSc) according to the criteria of the American Rheumatism Association[15] and the classification of LeRoy, *et al*[16]. Skin thickness was assessed using the modified Rodnan total skin thickness score (maximum possible score: 51)[17]. We excluded patients who had overlap syndrome with systemic lupus erythematosus (SLE), polymyositis (PM), or dermatomyositis (DM), diagnosed according to the American College of Rheumatology revised criteria for the classification of SLE[18] or the definite or probable criteria of Bohan and Peter for the classification of PM or DM[19,20].

Assessment of clinical characteristics. We estimated disease severity using a disease severity scale established by Medsger, *et al*[21]. Severe GIT involvement was defined as the presence of malabsorption syndrome, episodes of pseudo-obstruction, and/or the need for parenteral hyperalimentation. Malabsorption syndrome was diagnosed by clinical features (diarrhea, weight loss, anemia, abdominal distention) and the measurement of 24-hour fecal fat excretion (abnormal range > 6 g/day). The episode of pseudo-obstruction was diagnosed by clinical manifestations (severe abdominal pain and distension, nausea, vomiting), and then was confirmed by plain and computed tomography scans to exclude mechanical causes of the symptom complex. In our study, group 1 consisted of patients with SSc who developed severe GIT involvement within 2 years of the first symptom (except Raynaud's phenomenon) of SSc. We compared clinical manifestations and laboratory data of these patients with those of 2 control groups: all SSc patients without severe GIT involvement (group 2), and patients without severe GIT involvement within 2 years of onset of SSc (group 3). All SSc patients were followed up for at least 2 years.

When admitted, all patients with SSc underwent several medical examinations, and the likelihood of need for treatment was determined. Gastroesophageal reflux disease was ascertained by barium esophagography using a multiphasic cine technique, and esophagitis was estimated with a gastrofiberscope. ILD was assessed by chest radiography, high-resolution computed tomography (HRCT) of the chest, and pulmonary function testing (forced vital capacity). All patients were assessed by echocardiography, and all patients with a right ventricular systolic pressure of more than 40 mmHg underwent right catheterization. Pulmonary arterial hypertension (PAH) was defined as a mean pulmonary artery pressure of 25 mmHg or more and a pulmonary capillary wedge pressure of 15 mmHg or less at rest. We evaluated patients for SSc-related cardiomyopathy using the following criteria: multiple patchy defects detected by ^{201}Tl scintigraphy; and arrhythmia (atrioventricular block, paroxysmal ventricular contraction, sick sinus syndrome) or ischemic changes revealed by electrocardiography, without a history of myocardial infarction or idiopathic cardiomyopathy. Scleroderma renal crisis (SRC) was defined as malignant arterial hypertension and/or rapidly progressive renal failure and/or microangiopathic hemolytic anemia (MHA). Patients with hypertension of recent onset without increases in serum creatinine levels or MHA were not categorized as having SRC. The diagnosis of myositis related with SSc was based on the clinical findings of muscular symptoms such as bilateral muscle weakness, elevated creatine kinase or aldolase levels, and electromyographic and/or magnetic resonance imaging abnormalities. However, a patient with PM or DM who fulfilled definite or probable criteria of the classification by Bohan and Peter[19,20] was excluded in our study.

Detection of autoantibodies. All patients in our study were tested for antinuclear antibodies (ANA) using indirect immunofluorescence (IIF) and HEp-2 cells as the antigen substrate (FANAwell autoantibody kit, Iatron Laboratories, Tokyo, Japan). The presence of anticentromere antibodies (anti-CENP) was determined by the distinctive IIF pattern on HEp-2 cells and by enzyme immunoassay (MESACUP-2 Test, Medical & Biological Laboratories, Nagoya, Japan). Anti–topoisomerase I, anti–U1-snRNP, anti–SSA, and anti–SSB antibodies (referred to as anti-topo I, anti-U1RNP, anti-SSA, and anti-SSB) were determined by double immunodiffusion (DID) against calf thymus extracts using commercially available kits (Medical & Biological Laboratories). RNA and protein immunoprecipitation assays were carried out to identify additional SSc-related and myositis-related autoantibodies, such as anti–RNA polymerase I/III (anti-RNApol), anti–U3-RNP, anti-Th/To, anti–PM-Scl, anti-Ku, anti–aminoacyl tRNA synthetase, and anti–signal recognition particle (SRP) antibodies[22,23].

Statistical analysis. Frequencies of autoantibodies and clinical manifestations were evaluated by Fisher's exact test or Wilcoxon's rank sum test, and differences were considered significant at $p < 0.05$.

RESULTS

Clinical manifestations. Clinical profiles of all 302 patients with SSc are shown in Table 1. As shown in Table 2, there were no significant differences in age and sex among the 3 groups. The ratio of dcSSc to lcSSc was significantly higher in group 1 than in group 2 ($p = 0.007$) or group 3 ($p = 0.04$).

Clinical features. To investigate the clinical characteristics of group 1, we compared the frequencies of esophagitis, ILD, PAH, cardiac involvement, and myositis in group 1 with those in groups 2 and 3. As shown in Table 3, the frequencies of

Table 1. Clinical profiles of 302 patients with systemic sclerosis.

Characteristic	
Age, median (range), yrs	53 (19–86)
Female, n (%)	264 (87.4)
TSS, median (range)	13 (2–46)
Cutaneous type, n (%)	
Limited	197 (65.2)
Diffuse	105 (34.8)
Disease duration, median (range), mos	36 (0–480)
Organ involvement, n (%)	
Interstitial lung disease	154 (51.0)
Cardiac involvement	53 (17.5)
Scleroderma renal crisis	3 (1.0)
Myositis	37 (12.3)
Gastrointestinal involvement	211 (70.0)
Antinuclear antibody, n (%)	274 (90.7)
Anti-topoisomerase-I antibody, n (%)	76 (25.2)
Anti-centromere antibody, n (%)	102 (33.8)
Anti U1-snRNP antibody, n (%)	48 (15.9)
Anti SSA antibody, n (%)	41 (13.6)
Anti SSB antibody, n (%)	4 (1.3)

Gastrointestinal involvement includes esophageal, gastric, and intestinal involvement. TSS: modified Rodnan total skin thickness score.

Table 2. Patient characteristics.

Variable	Group 1, n = 14	Group 2, n = 288	p*	Group 3, n = 117	p**
Age, median (range), yrs	45 (26–71)	54 (19–86)	NS	53 (19–85)	NS
Female gender, n (%)	12 (85.7)	252 (87.5)	NS	102 (87.2)	NS
Cutaneous type, n (%)					
Limited	4 (28.6)	193 (67.0)	0.007	70 (60.0)	0.04
Diffuse	10 (71.4)	95 (33.0)		47 (40.0)	
Average duration of followup, mo	64.3	70.7	NS	68.8	NS

* Group 1 vs 2; ** Group 1 vs 3. P < 0.05 was considered significant. Age, female population, and followup duration differences were evaluated by Wilcoxon's rank sum test. Cutaneous type differences were evaluated by Fisher's exact test. NS: not significant; Group 1: patients with SSc who developed severe GIT involvement within 2 years of onset of SSc; Group 2: all remaining SSc patients, Group 3: SSc patients without severe GIT involvement within 2 years of onset of SSc.

Table 3. Frequencies of visceral involvement. Values indicate number (%) of patients.

	Group 1, n = 14	Group 2, n = 288	p*	Group 3, n = 117	p**
Interstitial lung disease	2 (14.3)	152 (52.8)	0.005	57 (48.7)	0.02
Esophagitis	7 (50.0)	43 (14.9)	0.003	19 (16.2)	0.002
Pulmonary arterial hypertension	0	21 (7.3)	NS	5 (4.3)	NS
Cardiac involvement	1 (7.1)	52 (18.0)	NS	20 (17.1)	NS
Myositis	6 (42.9)	31 (10.7)	0.003	15 (12.8)	0.01

* Group 1 vs 2; ** Group 1 vs 3. p < 0.05 was considered significant using Fisher's exact test. NS; not significant.

esophagitis and myositis were significantly higher in group 1 than in group 2 (p = 0.003 and p = 0.003, respectively) or group 3 (p = 0.002 and p = 0.01, respectively). In contrast, the frequency of ILD was significantly higher in group 2 (p = 0.005) and group 3 (p = 0.02), compared with group 1. There were no significant differences in the frequencies of PAH and cardiac involvement among the 3 groups. There were only 3 patients with SRC in group 2 and 1 patient in group 3; no patients in group 1 had SRC.

Detection of autoantibodies. Although there was no difference in the frequency of ANA among the 3 groups, the frequency of ANA with nucleolar staining by IIF was significantly higher in group 1 than in group 2 (p = 0.002) or group 3 (p = 0.01), as shown in Table 4. On the other hand, ANA showing discrete speckled staining were not observed in group 1, which reflects the fact that the frequency of anti-CENP was significantly higher in group 2 and group 3 versus group 1, as shown in Table 5. There were no significant differences in frequencies of anti–topo I, anti-U1RNP, anti-SSA, and anti-SSB among the 3 groups (Table 5). We found that the percentage of patients who were positive for either anti–topo I or anti-CENP was significantly lower in group 1 versus group 2 (group 1: 14.3%; group 2: 61.1%; p = 0.001) or group 3 (48.7%, p = 0.02). Because 2 major antibodies (anti–topo I and anti-CENP) observed in SSc were significantly less frequent in group 1, we investigated the other autoantibodies observed in SSc by immunoprecipitation: anti-U3RNP, anti-Ku, anti-Th/To, anti-RNApol, anti-PM-Scl, and so on. As shown in Table 6, a total of 5 patients in group 1 had anti-U3RNP, 1 patient in group 1 had anti-Ku, and 1 patient in group 1 had anti-SRP. Anti-RNApol was not noted in any patients in group 1.

Clinical features, natural history, and survival in the 14 patients with severe GIT involvement. Of the 14 patients with severe GIT involvement, 10 had pseudo-obstruction and 4 exhibited malabsorption. Three of the 10 patients with pseudo-obstruction also had malabsorption, and 2 of the 10 patients with pseudo-obstruction had pneumatosis cystoides intestinalis (PCI). Treatment for severe GIT involvement was administration of antibiotics to inhibit bacterial overgrowth and prokinetic drugs to improve pseudo-obstruction. One patient with pseudo-obstruction, PCI, and malabsorption died within 6 years after onset of GIT involvement because of bacterial peritonitis. During followup (mean: 64.3 mos), visceral manifestations of SSc other than GIT symptoms did not develop.

DISCUSSION

In our study, we demonstrated clinical features of SSc patients with severe GIT involvement in the early stage (less than 2 yrs from onset). Ours is the first report concerning severe GIT

Table 4. Antinuclear antibody (ANA) staining patterns. Values indicate number (%) of patients.

	Group 1, n = 14	Group 2, n = 288	p*	Group 3, n = 117	p**
ANA	12 (85.7)	262 (91.0)	NS	106 (90.6)	NS
ANA titer, median (range)	5120 (0–20, 480)	640 (0–40,960)		640 (0–40,960)	
ANA pattern					
Homogeneous	6 (42.9)	85 (29.5)	NS	32 (27.4)	NS
Speckled	3 (21.4)	118 (41.0)	NS	53 (45.3)	NS
Nucleolar	7 (50.0)	39 (13.5)	0.002	21 (17.9)	0.01
Discrete speckled	0	83 (28.8)	0.01	26 (22.2)	NS

* Group 1 vs 2; ** Group 1 vs 3. $p < 0.05$ was considered significant using Fisher's exact test. NS; not significant.

Table 5. Frequencies of specific autoantibodies. Values indicate number (%) of patients.

	Group 1, n = 14	Group 2, n = 288	p*	Group 3, n = 117	p**
Anti-topoisomerase I ab	2 (14.3)	74 (26.0)	NS	24 (20.5)	NS
Anti-centromere ab	0	102 (35.4)	0.003	33 (28.2)	0.02
Anti-U1-snRNP ab	1 (7.1)	47 (16.3)	NS	20 (17.1)	NS
Anti-SSA ab	0	41 (14.2)	NS	19 (16.2)	NS
Anti-SSB ab	0	4 (1.4)	NS	1 (0.8)	NS
Rheumatoid factor	2 (14.3)	116 (40.3)	NS	45 (38.5)	NS
Anti-double-strand DNA ab	0	12 (4.2)	NS	9 (7.7)	NS

* Group 1 vs 2; ** Group 1 vs 3. $p < 0.05$ was considered significant using Fisher's exact test. ab: antibody; NS; not significant.

Table 6. Analysis of specific autoantibodies by immunoprecipitation in group 1.

Patient	ANA Titer	ANA Pattern	Autoantibody	Clinical Features
1	160	Nu	U3RNP	My, Es
2	20480	Nu	U3RNP	Es
3	5120	Ho, Nu	U3RNP	My
4	20480	Nu	U3RNP	My, Es
5	640	Nu	U3RNP	My
6	10240	Ho, Sp	SRP	ILD
7	1280	Ho	topo I, U1RNP	My
8	10240	Ho, Nu	topo I, Ku	My, Es
9	80	Sp	ND	Ca
10	320	Ho	ND	ILD, Es
11	2560	Ho	ND	Es
12	10240	Sp, Nu	ND	Es
13	< 40	NA	ND	
14	< 40	NA	ND	

Interstitial lung disease (ILD), esophagitis with gastroesophageal reflux disease (Es), cardiac involvement (Ca), and myositis (My) were mentioned as clinical features. ANA: antinuclear antibody; Ho: homogeneous pattern; Ku: anti-Ku antibody; Nu: nucleolar pattern; Sp: speckled pattern; SRP: anti-signal recognition particle antibody; topo I: anti-topoisomerase I antibody; U1RNP: anti-U1-snRNP antibody; U3RNP: anti-U3-snRNP antibody; NA: not applicable; ND: not determined.

involvement in patients with SSc. As expected, a major proportion of these patients exhibited the diffuse cutaneous type; however, the frequency of ILD was significantly lower in group 1 [2 (14.2%) of 14 patients] than in group 2 or group 3. Moreover, ILD in these 2 patients was mild, corresponding to the low score on the disease severity scale established by Medsger, *et al*[21]. All patients were consecutively followed up at outpatient clinics for more than 2 years after study entry. Chest HRCT revealed no progression of ILD in these 2 patients, and the other patients did not develop ILD during fol-

lowup. Our results strongly suggest that severe GIT involvement is inversely correlated with the incidence of ILD in SSc, although a major subset of group 1 had the diffuse cutaneous type. Steen and Medsger[14] found severe GIT involvement in only about 4% of 935 patients with dcSSc 3 years from onset, and in 8% by 9 years. The prevalence of SSc with early severe GIT involvement in that trial was consistent with the prevalence in our study (4.6%), although patients with lcSSc were also included in our study. Our findings suggest that patients with severe GIT involvement represent a special group among patients with dcSSc and a low incidence of ILD.

Autoantibodies are noted in more than 90% of patients with SSc and are reported to be useful predictors of the complications and severity of tissue fibrosis and endothelial damage[24,25]. Both anti–topo I and anti-CENP are well known to be SSc-related autoantibodies and are frequently found in patients with SSc. In particular, anti–topo I is a useful indicator for the diffuse cutaneous type, and anti-CENP for the limited cutaneous type[26-28]. In our study, although there was a significant difference in the ratio of dcSSc to lcSSc between group 1 and the other patients, there was no significant difference in the frequency of anti–topo I between the 2 groups. On the other hand, anti-CENP was not present at all in group 1. The percentage of patients who were positive for either anti–topo I or anti-CENP was significantly lower in group 1. Given these findings, we speculated that other or unknown antibodies might be associated with the pathogenic process of developing early severe GIT involvement in SSc. Unfortunately, only 3 SSc-related autoantibodies (anti–topo I, anti-CENP, and anti-U1RNP) could be studied using routine laboratory examinations, DID or ELISA, performed at the Institute of Rheumatology, Tokyo Women's Medical University School of Medicine. Although it was impossible to evaluate autoantibodies in all 302 patients by immunoprecipitation because sera from all patients were not available, sera from 14 patients in group 1 were preserved and were further investigated using immunoprecipitation. As expected, we found specific antibodies in 7 patients in group 1: anti-U3RNP in 5 patients, anti-Ku in 1 patient, and anti-SRP in 1 patient. Further, both patients with anti–topo I in group 1 also had another ANA (anti-U1RNP or anti-Ku). The frequency of anti-U3RNP in group 1 (35.7%) is higher than in previous reports, including a study of Japanese patients (3%–7%)[23,29,30]. Anti-Ku, anti-SRP, and anti-U3RNP, as well as anti-U1RNP, are reported to be associated with myositis[29-34] and were present in 57% of group 1, as shown in Table 6. The frequency of myositis was significantly higher in group 1 than in group 2. Given our findings, it may be that smooth muscle injury in the GIT plays a crucial role in the development of severe GIT involvement. However, no specific ANA was found in 43% of patients in group 1, 2 of whom were negative for ANAs by IIF. There are several reports about the relationship between GIT involvement and anticytoplasmic antibodies such as anti–type 3 muscarinic acetylcholine receptor antibody[9] and antineuronal antibody[35-37]. It is possible that half of all patients with severe GIT involvement have anticytoplasmic antibody and neural degeneration.

Inconsistent with our results, anti-U3RNP has been reported to occur with high frequency in SSc patients with severe ILD[25,38]. In contrast, Kuwana, *et al*[39] reported that the frequency of ILD in Japanese SSc patients with anti-U3RNP was significantly lower than that in SSc patients without anti-U3RNP. This discrepancy could be due in part to ethnicity.

We determined the clinical characteristics of a small subset of patients with SSc and severe GIT involvement, especially involvement of the small intestine and colon. These patients exhibited GIT involvement as a principal symptom of SSc-related manifestations since the early stage, near the time of onset; in contrast, their disease was scarcely associated with ILD, PAH, or renal failure. Autoantibodies in the subset of patients with SSc were specific, unique ANA and were myositis-related antibodies; they included anti-U1RNP, anti-U3RNP, anti-SRP, and anti-Ku antibodies. These findings suggest that severe GIT involvement may result from injury of intestinal smooth muscle. However, 50% of patients in the subset did not have any specific autoantibodies, and further investigations are necessary to reveal a novel autoantibody and to examine the pathophysiology of intestinal muscles.

REFERENCES

1. Medsger TA Jr. Systemic sclerosis (scleroderma): clinical aspects. In: Koopman WJ, editor. Arthritis and allied conditions. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:1590-624.
2. Weinstein WM, Kadell BM. The gastrointestinal tract in systemic sclerosis. In: Clements PJ, Furst DE, editors. Systemic sclerosis. Philadelphia: Lippincott Williams & Wilkins; 2004:293-308.
3. Boeckxstaens GE, Bartelsman JFWM, Lauwers L, Tytgat GNJ. Treatment of GI dysmotility in scleroderma with the new enterokinetic agent prucalopride. Am J Gastroenterol 2002; 97:194-7.
4. Rose S, Young MA, Reynolds JC. Gastrointestinal manifestations of scleroderma. Gastroenterol Clin North Am 1998;27:563-94.
5. Rosson RS, Yesner R. Peroral duodenal biopsy in progressive systemic sclerosis. N Engl J Med 1965;272:391-4.
6. Greenberger NJ, Dobbins WO, Buppert RD. Intestinal atony in progressive systemic sclerosis (scleroderma). Am J Med 1968;45:301-8.
7. Malandrini A, Selvi E, Villanova M, et al. Autonomic nervous system and smooth muscle cell involvement in systemic sclerosis: ultrastructural study of 3 cases. J Rheumatol 2000;27:1203-6.
8. Goldblatt F, Gordon TP, Waterman SA. Antibody-mediated gastrointestinal dysmotility in scleroderma. Gastroenterology 2002;124:1144-50.
9. Sjogren RW. Gastrointestinal motility disorders in scleroderma. Arthritis Rheum 1994;37:1265-82.
10. Bassotti G, Battaglia E, Debernardi V, et al. Esophageal dysfunction in scleroderma: relationship with disease subsets. Arthritis Rheum 1997;40:2252-9.
11. Wegener M, Adamek RJ, Wedmann B, Jergas M, Altmeyer P. Gastrointestinal transit through esophagus, stomach, small and large intestine in patients with progressive systemic sclerosis. Dig Dis Sci 1994;39:2209-15.
12. Weston S, Thumshirn M, Camilleri M. Clinical and upper

gastrointestinal motility features in systemic sclerosis and related disorders. Am J Gastroenterol 1998;93:1085-9.
13. Jaovisidha K, Csuka ME, Almagro UA, Soergel KH. Severe gastrointestinal involvement in systemic sclerosis: report of five cases and review of the literature. Semin Arthritis Rheum 2004;34:689-702.
14. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000; 43:2437-44.
15. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.
16. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.
17. Clements PJ, Lachenbruch P, Seibold JR, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995;22:1281-5.
18. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
19. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344-7.
20. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975;292:403-7.
21. Medsger TA Jr, Silman AJ, Steen VD, et al. A disease severity scale for systemic sclerosis: development and testing. J Rheumatol 1999;26:2159-67.
22. Kuwana M, Okano Y, Pandey JP, Silver RM, Fertig N, Medsger TA Jr. Enzyme-linked immunosorbent assay for detection of anti–RNA polymerase III antibody. Arthritis Rheum 2005;52:2425-32.
23. Kuwana M, Kaburaki J, Okano Y, Tojo T, Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. Arthritis Rheum 1994;37:75-83.
24. Muhlen CA, Tan EM. Autoantibodies in the diagnosis of systemic rheumatic diseases. Semin Arthritis Rheum 1995;24:323-58.
25. Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum 2005;35:35-42.
26. Hesselstrand R, Scheja A, Shen GQ, Wiik A, Åkesson A. The association of antibodies with organ involvement and survival in systemic sclerosis. Rheumatology Oxford 2003;42:534-40.
27. Harris ML, Rosen A. Autoimmunity in scleroderma: the origin, pathogenetic role, and clinical significance of autoantibodies. Curr Opin Rheumatol 2003;15:778-84.
28. Senecal JL, Hénault J, Raymond Y. The pathogenic role of autoantibodies to nuclear autoantigens in systemic sclerosis (scleroderma). J Rheumatol 200;32:1643-9.
29. Arnett FC, Reveille JD, Goldstein R, et al. Autoantibodies to fibrillarin in systemic sclerosis (scleroderma). An immunogenetic, serologic, and clinical analysis. Arthritis Rheum 1996;39:1151-60.
30. Okano Y, Steen VD, Medsger TA Jr. Autoantibody to U3 nucleolar ribonucleoprotein (fibrillarin) in patients with systemic sclerosis. Arthritis Rheum 1992;35:95-100.
31. Cepeda EJ, Reveille JD. Autoantibodies in systemic sclerosis and fibrosing syndromes: clinical indications and relevance. Curr Opin Rheumatol 2004;16:723-32.
32. Satoh T, Okano T, Matsui T, et al. Novel autoantibodies against 7SL RNA in patients with polymyositis/dermatomyositis. J Rheumatol 2005;32:1727-33.
33. Kao AH, Lacomis D, Lucas M, Fertig N, Oddis CV. Anti–signal recognition particle autoantibody in patients with and patients without idiopathic inflammatory myopathy. Arthritis Rheum 2004;50:209-15.
34. Franceschini F, Cavazzana I, Generali D, et al. Anti-Ku antibodies in connective tissue diseases: clinical and serological evaluation of 14 patients. J Rheumatol 2002;29:1393-7.
35. Eaker EY, Kuldau JG, Verne GN, Ross SO, Sallustio JE. Myenteric neuronal antibodies in scleroderma: passive transfer evokes alterations in intestinal myoelectric activity in a rat model. J Lab Clin Med 1999;133:551-6.
36. Howe S, Eaker EY, Sallustio JE, Peebles C, Tan EM, Williams RC Jr. Antimyenteric neuronal antibodies in scleroderma. J Clin Invest 1994;94:761-70.
37. Reynolds JC. Immune-mediated enteric neuron dysfunction in scleroderma. J Lab Clin Med 1999;133:523-4.
38. Aggarwal R, Lucas M, Fertig N, Oddis CV, Medsger TA Jr. Anti-U3RNP autoantibody in systemic sclerosis (SSc): classification, demographics, clinical and laboratory features, natural history and survival in a series of 110 patients. Arthritis Rheum 2006;54 Suppl:S485.
39. Kuwana M, Okano Y, Kaburaki J, Tojo T, Medsger TA Jr. Racial differences in the distribution of systemic sclerosis–related serum antinuclear antibodies. Arthritis Rheum 1994;37:902-7.